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Tetrahedron: *Asymmetry*

Conformational control by remote stereogenic centers: linear tetrapyrroles

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Abstract—A novel, optically-active N_{21}–N_{22}, N_{23}–N_{24} bis-carbonyl-bridged bilirubin congener **1** with propionic acids replaced by *sec*-butyls exhibits a strong negative exciton chirality circular dichroism spectrum from the (*S*,*S*)-enantiomer. Molecular dynamics calculations favor the ***M***-helical diastereomer by 0.4 kJ/mol over the ***P***. The dipyrrinone model **2** of one half of **1** exhibits an almost undetectable circular dichroism. Unlike **1**, which is only very weakly fluorescent, **2** is strongly fluorescent, with quantum yield $\phi_F \sim 0.70$.

1. Introduction

Conversion of dipyrrinones, such as kryptopyrromethenone (Fig. 1A), which are not fluorescent, to intensely fluorescent *N*,*N*-carbonyl-bridged derivatives (e.g., kryptoglow, Fig. 1A) has been accomplished in high yield by reaction with 1,1′-carbonyldiimidazole (CDI) in the presence of a non-nucleophilic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2.[1,2] Dipyrrinones form strongly intermolecularly hydrogen-bonded dimers in CH_2Cl_2 (Fig. 1A);[3,4] the *N*,*N*-carbonyl-bridged analogues cannot. From such dimers, weak exciton coupling occurs, as evidenced by the weak bisignate circular dichroism (CD) spectra seen from solutions of optically active dipyrrinones in CH_2Cl_2.[5] Optically active *N*,*N*-carbonyl-bridged dipyrrinones should not be able to form dipyrrinone dimers and thus not exhibit exciton CD, yet two covalently-linked bridged dipyrrinones might. Solutions of the carbonyl-bridged dipyrrinones should be intensely fluorescent, while those of the latter should be only weakly fluorescent due to energy-transfer fluorescence quenching. In order to examine these hypotheses, we synthesized a new, optically active *N*,*N*-carbonyl-bridged bis-dipyrrinone **1** and dipyrrinone **2** (Fig. 1B).

2. Results and discussion

2.1. Synthesis

Reaction of dipyrrinones with CDI, catalyzed by DBU in CH_2Cl_2 typically led smoothly and in high yield to the *N*,*N*-carbonyl-bridged dipyrrinones. Conversion of the known dipyrrinone **4**[6] to **2** (in 89% yield) proved no exception. Whether both dipyrrinones of a bis-dipyrrinone, such as the previously reported bilirubin analogue,[6] could be bridged similarly was previously unknown. Although lactam to lactam bridging or pyrrole to pyrrole bridging might be viewed as possible alternatives, an 86% yield of **1** was achieved.

2.2. Characterization

The starting dipyrrinone **4** and bis-dipyrrinone **3** are known, including the absolute stereochemistry, from previous studies.[6] Two characteristic changes in the NMR spectra distinguish products from reactants: the presence of a new carbonyl group, imide type near 143 ppm in the ^{13}C NMR spectrum and the absence of pyrrole and lactam NH resonances in the ^{1}H NMR (Table 1). Unlike the 'carbonylation' reactions of **4** (to **2**), there is an alternate bis-*N*,*N*-bridged structure to **1**: one involving a carbonyl bridge between the two pyrrole rings and a second carbonyl bridge between the two lactam rings. Since the two new carbonyls of such a structure are predicted to exhibit different carbonyl signals in the ^{13}C NMR spectrum, whereas only

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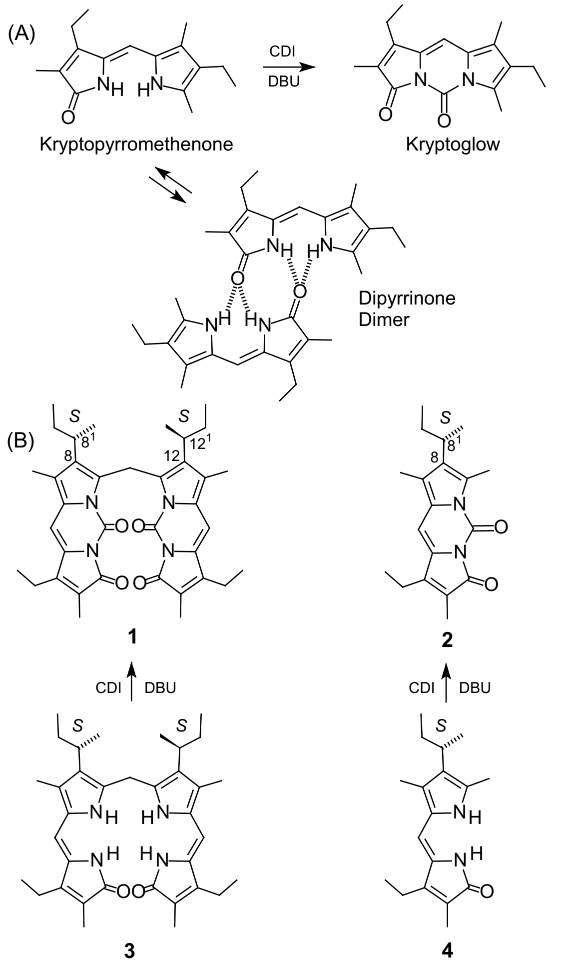
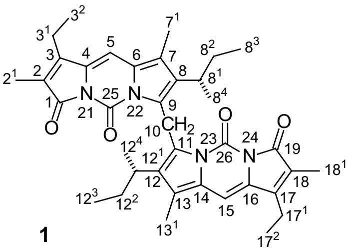


Figure 1. (A) Kryptopyrromethenone, its conversion to its *N*,*N*-carbonyl-bridged derivative, kryptoglow (by reaction with 1,1′-carbonyldiimidazole), and its monomer–dimer equilibrium. The dimer is favored in nonpolar solvents ($K_{assoc} \sim 30{,}000$ at 25 °C in $CDCl_3$). (B) Conversion of dipyrrinone **4** to its *N*,*N*-carbonyl-bridged derivative **2** and conversion of the bis-dipyrrinone analogue to its doubly carbonyl-bridged derivative **1**.

Table 1. ^{13}C NMR chemical shifts (ppm)[a] and assignments of carbons in **1**–**4**



Carbon		1	3[b]	2	4[b]
1, 19	C=O	167.6	174.1	167.8	174.0
2, 18	=C—	126.2	124.1	126.0	124.7
2^1, 18^1	CH_3	8.4	7.5	8.4	8.5
3, 17	=C—	146.2	146.7	146.3	148.3
3^1, 17^1	CH_2	17.9	17.8	17.9	18.0
3^2, 17^2	CH_3	13.8	14.7	13.8	15.1
4, 16	=C—	131.5	128.6	131.1	126.8
5, 15	=CH—	96.6	100.0	96.8	101.2
6, 14	=C—	130.4	123.3	130.1	122.2
7, 13	=C—	120.4	122.1	120.5	122.0
7^1, 13^1	CH_3	10.9	11.1	10.4	10.3
8, 12	=C—	127.4	124.2	126.6	124.9
8^1, 12^1	CH	31.8	33.1	32.4	32.7
8^2, 12^2	CH_2	28.6	29.6	28.9	29.6
8^3, 12^3	CH_3	12.5	12.9	13.2	12.7
8^4, 12^4	CH_3	19.1	20.7	20.0	20.6
9, 11	=C—	132.9	131.0	131.3	131.2
$10/9^1$	CH_2/CH_3	25.6	23.2	12.6	12.8
25, 26	C=O	143.1	—	143.5	—

[a] In ppm downfield from $(CH_3)_4Si$ for 1×10^{-2} M solutions in $CDCl_3$ at 22 °C.

[b] Entries for **3** and **4** obtained from Ref. 6.

one is seen, structure **1** seems the more logical fit to the NMR data (Table 1). A similar geometry-governed regioselectivity has been reported in the carbonylation reaction (using phosgene) of a simple corrole where the –CO– bridge is formed on the dipyrromethine fragment rather than on the bipyrrole fragment.[7]

Unlike the starting tetrapyrrole **3** and dipyrrinone **4** (Fig. 1B), which are dimeric in $CHCl_3$,[6,8] with the dimers held together by intermolecular hydrogen bonding of the type depicted in Figure 1A, both **1** and **2** are monomeric in $CHCl_3$, as determined by vapor pressure osmometry (VPO): **1**: measured MW 607 ± 8 (FW 609 g/mol) and **2**: measured MW 302 ± 10 (FW 312 g/mol). This result might be expected from the total absence of NH groups in **1** and **2**, used in their unbridged predecessors in forming intermolecularly hydrogen-bonded dimers. There is thus no evidence for π-stacking interactions leading to self-association.

On silica gel TLC chromatographic analysis using 1% CH_3OH in CH_2Cl_2 (v/v), **1** (R_f 0.44) moves faster than **3** (R_f 0.30), and **2** (R_f 0.79) moves much faster than **4** (R_f 0.49)—again consistent with the absence of NH groups. Both **1** and **2** are also much more soluble than are **3** and **4** in nonpolar solvents, such as hexane or benzene.

2.3. Fluorescence and circular dichroism spectra

As shown in Figure 2, **2** is intensely fluorescent (ϕ_F 0.70, $CHCl_3$) in contrast to its dipyrrinone precursor **4**, which is only weakly fluorescent ($\phi_F < 0.01$). Also, as seen in Figure 2A, **2** exhibits a weak baseline CD curve for the long wavelength transition, while that of **4** is undetectable.

Unlike dipyrrole **2**, tetrapyrrole **1** is only weakly fluorescent in $CHCl_3$ (fluorescence quantum yield $\phi_F = 0.09$), although the ϕ_F is higher in cyclohexane (0.19), with fluorescence quenching in the bis-chromophore apparently coming from intramolecular energy transfer, as might be expected. Also unlike **2**, the CD $\Delta\varepsilon$ values of **1** are large and the curves bisignate (Fig. 2B). The tetrapyrrole precursor **3** to **1** also exhibits a moderately intense CD couplet, but in **3** the Cotton effect intensities drop with increasing solvent polarity (Table 2).

Bis-dipyrrinone **3**, the precursor of **1**, is an enantiomerically pure all-alkyl substituted rubin. It has been used

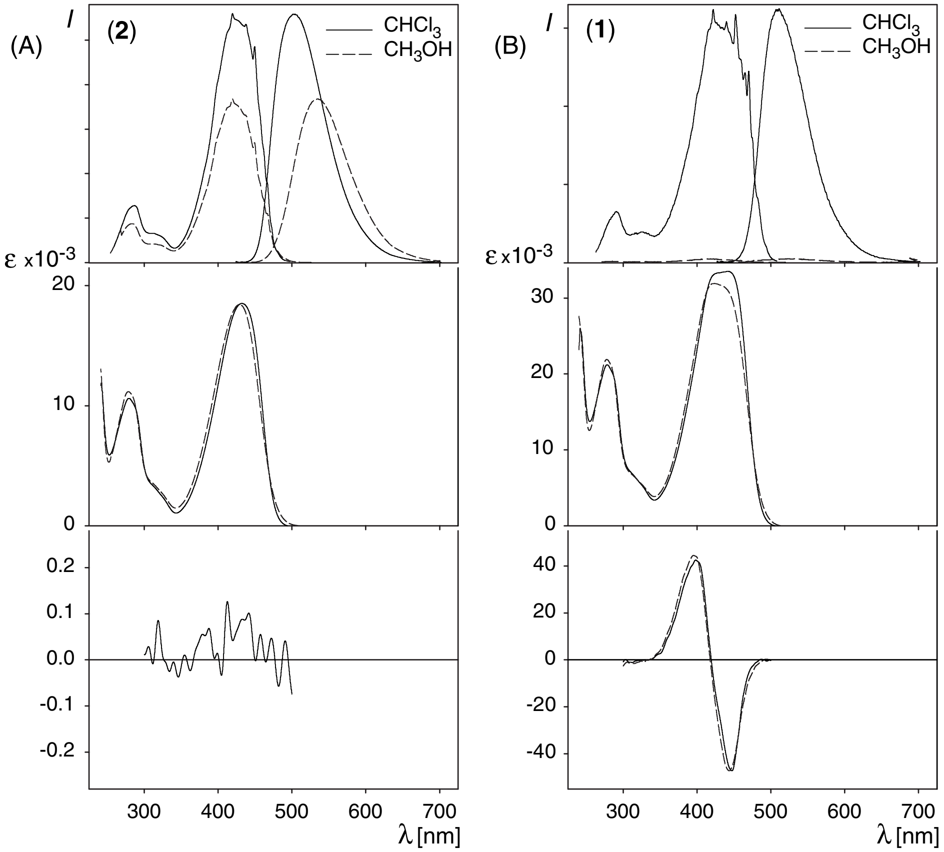


Figure 2. Fluorescence excitation and emission (top), UV–vis (middle) and CD spectra (bottom) of (A) dipyrrinone **2** and (B) doubly-bridged bis-dipyrrinone **1** in $CHCl_3$ and in CH_3OH.

Table 2. Comparisons of CD spectral data from 1.5×10^{-5} M solutions of **1** and **3**

Solvent	ε[a]	**1**			**3**		
		$\Delta\varepsilon_1^{max}$ (λ, nm)	$\Delta\varepsilon = 0$ (λ, nm)	$\Delta\varepsilon_2^{max}$ (λ, nm)	$\Delta\varepsilon_1^{max}$ (λ, nm)	$\Delta\varepsilon = 0$ (λ, nm)	$\Delta\varepsilon_2^{max}$ (λ, nm)
Cyclohexane	2.0	−51 (439)	413	+44 (396)	−46 (440)	393	+50 (372)
Benzene	2.3	−51 (443)	416	+45 (398)	−45 (440)	394	+43 (374)
$CHCl_3$	4.7	−47 (447)	419	+43 (398)	−40 (433)	394	+42 (373)
EtOAc	6.0	−50 (439)	413	+47 (393)	−40 (432)	392	+46 (370)
$(CH_3)_2CO$	20.7	−51 (439)	414	+47 (393)	−41 (425)	392	+45 (370)
CH_3CN	36.2	−53 (440)	413	+47 (395)	−38 (429)	392	+42 (370)
CH_3OH	32.6	−47 (444)	418	−45 (395)	−20 (430)	403	+17 (382)
CF_3CH_2OH		−39 (448)	423	+36 (402)	−13 (400)	409	+11 (375)
$HCONHCH_3$	181.2	−55 (447)	420	+49 (399)	−21 (432)	403	+17 (387)
$HCON(CH_3)_2$	36.7	−54 (442)	416	+51 (396)	−24 (425)	395	+18 (376)
$(CH_3)_2SO$	46.5	−55 (443)	418	+52 (397)	−30 (428)	398	+20 (386)
CH_3COOH		−46 (446)	420	+43 (396)	−22 (429)	397	+19 (389)

[a] Dielectric constants from Ref. 13.

previously to probe the background optical activity in bilirubin-like molecules lacking the conformation-stabilizing intramolecular hydrogen-bonding forces, intrinsic to the corresponding diacid (Fig. 3A).[6] The last has β-methyl groups, which act in a gear-like fashion to direct the preferred ridge-tile conformation of ***M***- or ***P***-helicity, depending upon the absolute configuration. The diacid rubin with a (β*S*,β′*S*)-configuration exhibits intense bisignate CD Cotton effects with $|\Delta\varepsilon| \sim 330$.[9] The corresponding dimethyl ester in chloroform exhibits $\Delta\varepsilon = -130.5$ (416 nm), $\Delta\varepsilon = +62.5$ (376 nm), which drops in methanol to $\Delta\varepsilon = -42.9$ (419 nm), $\Delta\varepsilon = +16.0$ (371 nm).[10] This dimethyl ester was found by vapor pressure osmometry (VPO) to be monomeric in chloroform at 45 °C. In contrast, absent acid and ester groups, **3** has an apparent molecular weight of 1115 in $CHCl_3$ (by VPO) versus the formula weight of 556.8.[8] Consequently, **3** exists in $CHCl_3$ at 45 °C as a dimer. It was therefore unclear whether its CD Cotton effects $\Delta\varepsilon = -40.1$ (433 nm), $\Delta\varepsilon = +42.2$ (373 nm) in $CHCl_3$, and $\Delta\varepsilon = -20.0$ (430 nm), $\Delta\varepsilon = +17.3$ (382 nm) in CH_3OH[6] originated solely from intramolecular exciton

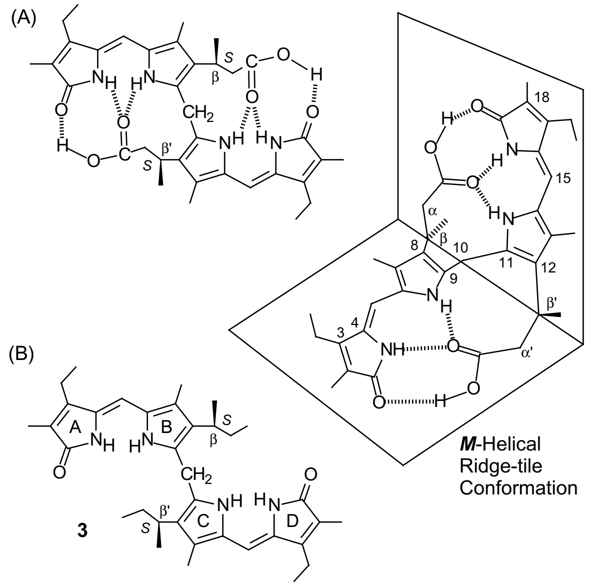


Figure 3. (A) Intramolecularly hydrogen-bonded (β*S*,β′*S*)-dimethylmesobilirubin-XIIIα shown in the planar projection (left) and in its most stable ***M***-helical ridge-tile conformation (right). (B) The hydrocarbon analogue **3** of (A), shown in planar projection. Although not stabilized by hydrogen bonding, the most favored conformation of **3** is still the ***M***-helicity ridge-tile (with no intramolecular hydrogen bonds).

coupling or whether they came from intermolecular interaction in the dimer.

The new carbonyl-bridged bis-dipyrrinone **1** (obtained from **3**) has no NH's and definitely cannot engage in intermolecular hydrogen bonding interactions leading to dimers—although π-stacking might contribute to dimer formation. VPO measurements in $CHCl_3$ at 45 °C, however, clearly showed the absence of dimers, while the CD spectra of **1** appear to rule out dimerization. The CD spectra were acquired in a variety of solvents, and the data (Table 2), significantly, show exciton Cotton effects with intensities that are almost independent of solvent polarity, for example, in $CHCl_3$ $\Delta\varepsilon = -47.2$ (447 nm), $\Delta\varepsilon = +42.5$ (398 nm); and in CH_3OH $\Delta\varepsilon = -47.3$ (444 nm), $\Delta\varepsilon = +44.5$ (395 nm). In nonpolar solvents, the long wavelength, broadened UV–vis band of **1** clearly shows two overlapped components, which are resolved in CD spectra (Fig. 2B). The longer wavelength part of the CD couplet is negative, which corresponds to a (β*S*,β′*S*) absolute configuration.

The CD intensity of **1** is almost as high as (or even higher in polar solvents than) that of its precursor **3**. Consequently, assuming monomeric **1** exhibits CD similar to that of the dimeric precursor rubin **3**, there is no basis for consideration of CD in **1** originating from intermolecular exciton interaction in a dimer. Polar solvents, like methanol, disrupt the dimers of **3**, and this is seen as diminishing its CD intensity by 50%. In contrast, **1** is incapable of dimerization (by intermolecular hydrogen bonding) and maintains a nearly constant CD intensity in nonpolar (cyclohexane) and polar (DMSO) solvents. The bridging carbonyls of **1** cause a ~15–25 nm bathochromic shift of the CD effects relative to the Cotton effects of **3**.

2.4. Conformation from molecular dynamics calculations

The identical chromophores of **1** conjoined by a methylene group are essentially planar as found by calculations using the SYBYL force field.[11] The angle between the dipyrrinone planes defined by the lactam and conjoined pyrrole rings (A–B and C–D in Fig. 3B) is 1.5° in **1**. In contrast, the angle is ~34° in the nonbridged parent **3**. A twisted dipyrrinone in **3** alleviates repulsion between the NHs when a hydrogen bond acceptor is absent from a side chain, for example, propionate, on the opposing dipyrrinone.

The important torsion angles defining the mutual loci of carbonyl-bridged dipyrrinones in **1** (or dipyrrinones of **3**) are ϕ_1 = N(22)–C(9)–C(10)–C(11) and ϕ_2 = C(9)–C(10)–C(11)–N(23). Both are found to be negative and identical $\phi_1 = \phi_2 = -57°$ in the global energy minimum conformation of **1** that corresponds to an ***M***-helicity ridge-tile secondary structure (Fig. 4). In this ***M***-helical conformer, one predicts a negative handedness (helicity) of the two long wavelength excited state electric transition dipole moments. According to the exciton chirality rule,[12] such helicity correlates well with the experimentally-observed, negative CD exciton couplet. It should be noted that the ***P***-helical ($\phi_1 = \phi_2 = +59°$) mirror image conformation of (*S*,*S*)-**1**, as computed by SYBYL,[11] lies only 0.4 kJ/mol higher in energy than the ***M***. This small energy difference suggests that the observed small CD amplitudes for this bichromophore arise from superposition of population-weighted contributions from energy close lying conformations.

In parallel, bis-dipyrrinone **3** with an (*S*,*S*) configuration is also computed (SYBYL) to prefer an ***M***-helical shape, with $\phi_1 = \phi_2 = -60°$; and, as in **1**, the calculated ***P***-helical (*S*,*S*)-**3** ($\phi_1 = \phi_2 = +73°$) is only slightly disfavored, by 0.4 kJ/mol over the ***M***-helical.

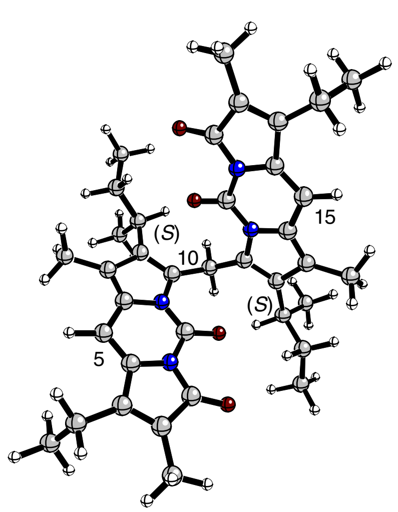


Figure 4. Ball and stick representation of the most stable conformation of **1**, as determined by molecular dynamics calculations.

3. Conclusions

An enantiomerically pure bilirubin congener lacking carboxylic acids is smoothly converted into an N_{21}–N_{22}, N_{23}–N_{24} bis-carbonyl-bridged bis-dipyrrinone by reaction with excess CDI in the presence of DBU. The new bichromophore rubin exhibits intense negative exciton chirality CD that originates from a monomeric species (as determined by VPO) that cannot engage in hydrogen bonding. The pigment's preferred conformation is governed by the absolute configuration of remote stereogenic centers, as confirmed by molecular mechanics calculations. In contrast to the mono-dipyrrinone fluorophore **2** (quantum yield $\phi_F = 0.83$ in cyclohexane), the bis-dipyrrinone fluorophore **1** has a much lower quantum yield ($\phi_F = 0.19$ in cyclohexane), presumably lowered by intramolecular quenching.

4. Experimental

4.1. General procedures

Nuclear magnetic resonance spectra were obtained on a Varian Unity Plus spectrometer at 11.75 T magnetic field strength operating at ^{1}H frequency of 500 MHz and ^{13}C frequency of 125 MHz. $CDCl_3$ solvent was used throughout with chemical shifts reported in δ ppm referenced to residual $CHCl_3$ ^{1}H signal at 7.26 ppm and $CDCl_3$ ^{13}C signal at 77.00 ppm. *J*-Modulated spin-echo (Attached Proton Test) and gHMBC experiments were used to obtain the ^{13}C NMR assignments. All UV–vis spectra were recorded on a Perkin–Elmer Lambda 12 spectrophotometer, fluorescence spectra were measured on a Jobin Yvon FluoroMax 3 instrument, and the circular dichroism spectra were recorded on a JASCO J-600 dichrograph. Vapor pressure osmometry measurements were performed on an OSMOMAT 070-SA instrument (Gonotec, GmbH) in acid free $CHCl_3$ at 45 °C. Radial chromatography was carried out on Merck silica gel PF_{254} with $CaSO_4$ binder preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA) with 1, 2, or 4 mm thick rotors and analytical thin-layer chromatography was carried out on J. T. Baker silica gel IB-F plates (125 μm layer). Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. The combustion analyses were carried out by Desert Analytics, Tucson, AZ.

4.2. General procedure for the cyclization to 1 and 2

A mixture of 1 mmol of pigment **3**[6] or **4**,[6] 1.62 g (10 mmol) of 1,1′-carbonyldiimidazole (5 mmol for **4**), 3.0 mL (10 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (5 mmol for **4**) and 350 mL of anhydrous CH_2Cl_2 (100 mL for **4**) was heated under N_2 at reflux for 3 h (16 h for **4**). After cooling, the mixture was washed with 1% aq HCl (2×50 mL), then with water (3×50 mL) and the solution dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent under vacuum, the residue was purified by radial chromatography on silica gel and recrystallized from ethyl acetate–hexane to afford bright yellow tricyclic pigments.

4.2.1. (+)-(8^1*S*)-1-Ethyl-8-(1-methylpropyl)-2,7,9-trimethyl-3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]-pyrimidine-3,5-dione 2. Compound **2** was isolated in 89% yield; mp 97–98 °C; ^{1}H NMR: δ 0.82 (3H, t, $J = 7.4$ Hz), 1.21 (3H, t, $J = 7.7$ Hz), 1.23 (3H, d, $J = 7.2$ Hz), 1.63 (2H, m), 1.95 (3H, s), 2.16 (3H, s), 2.53 (2H, q, $J = 7.7$ Hz), 2.66 (3H, s), 2.70 (1H, m), 6.39 (1H, s) ppm; $[\alpha]_D^{20} = +25.4$ (*c* 0.22, $CHCl_3$). UV–vis: ε^{max} (λ) 18,500 (432 nm), 10,600 (279 nm) ($CHCl_3$); 18,400 (429 nm), 11,200 (278 nm) (CH_3OH). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.29; H, 7.55; N, 9.06.

4.2.2. (−)-(*S*,*S*)-Bis-[1-ethyl-8-(1-methylpropyl)-2,9-dimethyl-3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]-pyrimidine-3,5-dione-7-yl]methane 1. Compound **1** was isolated in 86% yield; mp 168–169 °C; ^{1}H NMR: δ 0.66 (6H, t, $J = 7.4$ Hz), 1.03 (6H, d, $J = 7.1$ Hz), 1.21 (6H, t, $J = 7.7$ Hz), 1.43, 1.48 (2×2H, $2 \times$ m), 1.94 (6H, s), 2.14 (6H, s), 2.42 (2H, m), 2.53 (4H, q, $J = 7.7$ Hz), 5.29 (2H, s), 6.40 (2H, s) ppm; $[\alpha]_D^{20} = -621.8$ (*c* 1.4×10^{-2}, $CHCl_3$). UV–vis: ε^{max} (λ) 33,500 (442 nm), 21,200 (278 nm) ($CHCl_3$); 31,900 (423 nm), 21,900 (278 nm) (CH_3OH). Anal. Calcd for $C_{37}H_{44}N_4O_4$: C, 73.00; H, 7.29; N, 9.20. Found: C, 72.66; H, 7.23; N, 9.21.

References

1. Brower, J. O.; Lightner, D. A. *J. Org. Chem.* **2002**, *67*, 2713–2716.
2. Boiadjiev, S. E.; Lightner, D. A. *J. Phys. Org. Chem.* **2004**, *17*, 675–679.
3. Falk, H. The Chemistry of Linear Oligopyrroles and Bile Pigments; Springer: Wien, 1989.
4. Nogales, D. F.; Ma, J.-S.; Lightner, D. A. *Tetrahedron* **1993**, *49*, 2361–2372.
5. Boiadjiev, S. E.; Anstine, D. T.; Lightner, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 8727–8736.
6. Boiadjiev, S. E.; Pfeiffer, W. P.; Lightner, D. A. *Tetrahedron* **1997**, *53*, 14547–14564.
7. Saltsman, I.; Goldberg, I.; Gross, Z. *Tetrahedron Lett.* **2003**, *44*, 5669–5673.
8. Boiadjiev, S. E.; Lightner, D. A. *J. Heterocycl. Chem.* **2000**, *37*, 863–870.
9. Boiadjiev, S. E.; Person, R. V.; Puzicha, G.; Knobler, C.; Maverick, E.; Trueblood, K. N.; Lightner, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10123–10133.
10. Boiadjiev, S. E.; Anstine, D. T.; Lightner, D. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1945–1964.
11. The molecular dynamics calculations used to find the global energy minimum conformation of **1** were run on an SGI Octane workstation using version 6.9 of SYBYL (Tripos Assoc., St. Louis, MO) as described in: Person, R. V.; Peterson, B. R.; Lightner, D. A. *J. Am. Chem. Soc.* **1994**, *116*, 42–49, The ball and stick drawings were created from the atomic coordinates using Müller and Falk's 'Ball and Stick' program for the Macintosh (http://www.orc.uni-Linz.ac.at/mueller/ball_stick.html).
12. Harada, N; Nakanishi, K. Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry; University Science Books: Mill Valley, CA, 1983.
13. Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; pp 4–8.